

F I N T COOPERATION TREA

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

| | |
|---|---|
| Date of mailing (day/month/year) 06 March 2001 (06.03.01) | |
| International application No. PCT/EP00/06185 | Applicant's or agent's file reference SCB555PCT |
| International filing date (day/month/year) 03 July 2000 (03.07.00) | Priority date (day/month/year) 06 July 1999 (06.07.99) |
| Applicant BOMBARDELLI, Ezio et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 January 2001 (17.01.01)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38 |
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REC'D 24 SEP 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference SCB555PCT | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP00/06185 | International filing date (day/month/year) 03/07/2000 | Priority date (day/month/year) 06/07/1999 |
| International Patent Classification (IPC) or national classification and IPC C07D493/08 | | |
| Applicant INDENA S.P.A. et al. | | |



- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 3 sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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|---|---|
| Date of submission of the demand 17/01/2001 | Date of completion of this report 20.09.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Helps, I Telephone No. +49 89 2399 8209  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06185

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-27 as originally filed

Claims, No.:

1-10 as received on 11/07/2001 with letter of 10/07/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06185

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|------|
| Novelty (N) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-10 |
| | No: | Claims | |

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/06185

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this report.

| | |
|--|------|
| US-A-5,750,562 | (A) |
| US-A-5,705,508 | (B) |
| Journal of Medicinal Chemistry, vol.40, p.267-78 (1997) | (C) |
| US-A-5,621,121 | (D) |
| US-A-5,476,954 | (E) |
| Tetrahedron, vol. 38, p.4273-6 (1997) | (F) |

The novel feature of claim 1 is the alpha-configuration of the hydroxy group at the 7-position. Claims 2-6 drawn to processes for the preparation of compounds of claim 1, as well as claims 9 and 10 drawn to pharmaceutical compositions containing compounds of claim 1 and the use of compounds of claim 1 for the preparation of medicaments are novel by consequence. The novel feature of claim 7 is the choice of leucinol as starting material for the preparation of the oxazolidinone-5-carboxylic acid, followed by the preparation of the cyanohydrin, conversion to a carboxylic acid ester and condensation with dimethoxybenzaldehyde dimethyl acetal. Claim 8 is rendered novel by the choice of substituents on the baccatine III, V or oxazolidinone-5-carboxylic acid ring systems.

Claims 1 to 10 therefore meet the Novelty requirements of Article 33(2) PCT.

The Applicant has submitted a comparative test which shows that the presently claimed 7-alpha epimer of the Baccatine III compound of claim 1 has improved bioavailability compared to the 7-beta epimer which is known from documents (B) and (C) (see annex to letter of 10.7.2001). This improvement would not have been predictable by the skilled man. Inventive step (Article 33(3)) is recognised because the problem of providing baccatine derivatives with improved bioavailability has been solved in a non-obvious manner. The intermediate compounds of claim 8 are also patentable insofar as they contribute a new structural feature to the end product of claim 1.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/06185

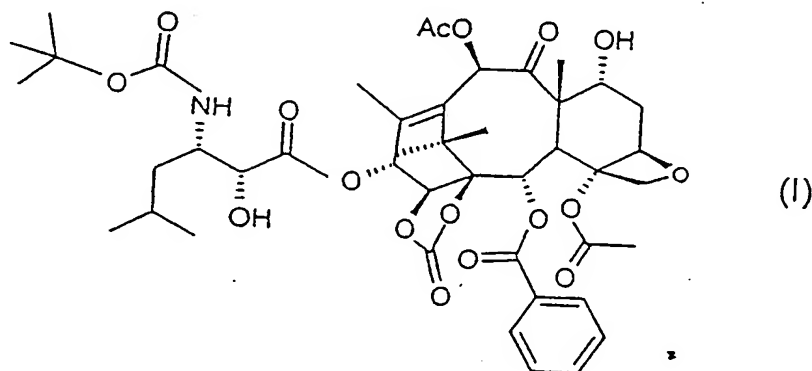
The process of claim 7 gives considerably higher yields than the prior art process of document (E), which is used to prepare similar oxazolidinone carboxylic acid derivatives (see page 1 paragraph 3 to page 2 paragraph 1 of the letter of 10.7.2001). Thus claim 7 also meets the requirements of Article 33(3) PCT.

VII CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document (A) is not mentioned in the description, nor is this document identified therein.

CLAIMS

1. Compound of formula (I):



2. A process for the preparation of the compound of formula (I), in which 13-(N-Boc- β -isobutylisoserinyl)-14 β -hydroxy-baccatine III 1,14-carbonate is either treated with DBU (diazabicyclo[5,4,0] 7-undecene) in methanol or THF, or alternatively is left in solution with methylene chloride or chlorinated solvents in the presence of aliphatic alcohols selected from methanol, ethanol or propanol and with basic allumine, for a time ranging from one hour to 14 days.

3. A process for the preparation of 13-(N-Boc- β -isobutylisoserinyl)-14 β -hydroxy-baccatine III or V 1,14-carbonate, which comprises the following steps:

- transformation of 14 β -hydroxy-10-deacetyl baccatine III or V into the triethylsilylated derivative at the 7-position;
- preparation of the 1,14 carbonate derivative from the product of step (a);
- selective acetylation of the hydroxyl at 10;
- reaction of the product of step (c) with (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid;

e) cleavage of the triethylsilyl and dimethoxybenzylidene protective groups from the product of step (d).

4. A process as claimed in claim 3, in which:

the silylating agent of step (a) is triethyl chlorosilane;
the 1,14 carbonate derivative in step (b) is prepared using
phosgene in toluene in methylene chloride/pyridine 3:1
solution under nitrogen atmosphere; the reduction of step
(c) is carried out with LiHMDS in anhydrous THF, and the
resulting 10-hydroxy derivative is subsequently acetylated
with acetyl chloride; the condensation reaction of step (d)
is carried out in anhydrous apolar organic solvent, in the
presence of a base and of the condensing agent
dicyclohexylcarbodiimide (DCC); the triethylsilyl
protective group in step (e) is removed with pyridinium
fluoride in acetonitrile/pyridine solution under nitrogen,
and the dimethoxybenzylidene protective group is removed in
methylene chloride solvent by addition of HCl in methanol
and subsequently of NaHCO_3 .

5. A process for the preparation of 13-(N-Boc- β -isobutylisoserinyl)-14 β -hydroxy-baccatine III or V 1,14-carbonate, which comprises the following steps:

a') selective acetylation of the hydroxyl at C-10 of 14 β -hydroxy-10-deacetylbaccatine III or V;

b') preparation of the 1,14 carbonate derivative from the product of step (a');

c') silylation of the hydroxyl at C-7;

d') reaction of the product of step (c) with (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid;

e') cleavage of the triethylsilyl and dimethoxybenzylidene protective groups from the product of step (d').

6. A process as claimed in claim 5, in which the selective acetylation of step (a') is carried out with acetic anhydride in the presence of cerium, scandium,

ytterbium salts, preferably $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, and steps (b')-(e') are carried out analogously to steps (b), (a), (d) and (e) of claim 4.

7. A process for the preparation of (4S, 5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid, which comprises the following steps:

- a) protection of the amino group of leucinol with Boc;
- b) transformation of N-Boc-L-leucinol into N-Boc-L-leucinal;
- 10 c) preparation of the cyanhydrin of the product of step (b);
- d) transformation of the cyanhydrine nitrile into the corresponding carboxylic acid;
- e) formation of the carboxylic acid methyl ester;
- 15 f) purification of the (2R, 3S)-3-(N-Boc)amino-2-hydroxy-5-methylhexanoic acid methyl ester;
- g) condensation of the product of step (f) with 2,4-dimethoxybenzaldehyde dimethyl acetal;
- h) transformation of (4S, 5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid methyl ester into the corresponding carboxylic acid.
- 20

8. The following synthesis intermediates: 14 β -hydroxy baccatine III or V, 14 β -hydroxy baccatine III or V 1,14 carbonate, 14- β -hydroxy-7-Tes-10-deacetyl baccatine III or V, 14- β -hydroxy-7-Tes-baccatine III or V, 14- β -hydroxy-7-Tes-baccatine III or V 1,14-carbonate, (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid.

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9. Pharmaceutical compositions containing compound (I) together with pharmaceutically acceptable carriers and excipients.

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10. The use of compound (I) for the preparation of a drug with anticancer activity.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

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| Applicant's or agent's file reference SCB555PCT | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/EP 00/ 06185 | International filing date (day/month/year) 03/07/2000 | (Earliest) Priority Date (day/month/year) 06/07/1999 |
| Applicant INDENA S.P.A. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/06185

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6,8(part),9-10

14-beta-hydroxy-1,14-carbonate baccatine V and processes for its preparation

2. Claims: 7,8(part)

(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid and process for its preparation.

INTERNATIONAL SEARCH REPORT

International Application No

PC 00/06185

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D493/08 A61K31/335 C07D263/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | US 5 705 508 A (OJIMA ET. AL.) 6 January 1998 (1998-01-06) cited in the application Figure 1, compound SB-T-101131, examples 63-74 | 1-6,8-10 |
| Y | I. OJIWA ET. AL.: "Synthesis and Structure-Activity Relationships of Taxoids Derived from 14-beta-Hydroxy-10-deacetylbaecatin III." JOURNAL OF MEDICINAL CHEMISTRY , vol. 40, no. 2, 17 January 1997 (1997-01-17), pages 267-78, XP002149586 page 270, Scheme 4, compound 22. -/-- | 1-6,8-10 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 December 2000

Date of mailing of the international search report

18.12.00

Name and mailing address of the ISA

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Authorized officer

Helps, I

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US 5 750 562 A (BOMBARDELLI ET. AL.) 12 May 1998 (1998-05-12) example 7 | 8 |
| Y | column 4, line 1 - line 46 --- | 1-6,8-10 |
| A | US 5 763 628 A (BOURZAT ET. AL.) 9 June 1998 (1998-06-09) claims; examples --- | 1-6,8-10 |
| X | G. APPENDINO ET. AL.: "Synthesis and Evaluation of C-seco-Paclitaxel Analogues." TETRAHEDRON LETTERS, vol. 38, no. 24, 1997, pages 4273-6, XP004074809 page 4274, lines 10-12, Scheme 1 --- | 8 |
| A | US 5 621 121 A (COMMERCON ET. AL.) 15 April 1997 (1997-04-15) column 5, line 65 -column 6, line 40 --- | 7 |
| A | US 5 476 954 A (BOURZAT ET. AL.) 19 December 1995 (1995-12-19) column 4, line 23 -column 6, line 10 ----- | 7 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/06185

| Pat nt document cted in search report | | Publication date | Patent family memb r(s) | Publication date |
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 00/06185

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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(54) Title: TAXANE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

(57) Abstract: A novel taxane derivative with anticancer activity, a process for its preparation and a process for the preparation of 14- β -hydroxy-1,14-carbonate-baccatine III and V derivatives 13-substituted by an isoserine residue.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D493/08 A61K31/335 C07D263/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6,8(part),9-10

14-beta-hydroxy-1,14-carbonate baccatine V and processes for its preparation

2. Claims: 7,8(part)

(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-isobutyl-1-oxazolidine-5-carboxylic acid and process for its preparation.

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